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(54) THE USE OF N-ACETYL-D-GLUCOSAMINE FOR PREPARING MEDICINES FOR UROGENITAL TRACT INFECTION'S TREATMENT AND PREVENTION

(57) The present invention discloses a use of N-acetyl-D-glucosamine in the manufacture of a medicament for treatment of urogenital tract infection. N-acetyl-D-glucosamine exhibits function of suppressing the transplantation of exotic microorganisms and promoting the repair of topical skin tissue, and the formulation comprising it as main active component is used for the prevention and treatment of urogenital tract infection and has advantages such as notable therapeutical effect, easy preparation, non-irritation, non-contamination, etc.

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Description

Technical field

[0001] The present invention relates to the use of N-acetyl-D-glucosamine in the manufacture of a medicament for treating urogenital tract infection.

Background Art

[0002] Urogenital tract infection is a common disease, which is chronic and refractory and greatly interferes a patient's normal life. At present, the main medicaments for treating urogenital tract infection mainly are broad spectrum antibiotics and Chinese lotion. However, the abuse of broad spectrum antibiotics results in drug resistance in microorganisms causing urogenital tract infection, so that the therapeutical effect became worse and worse although the dose of antibiotics increases gradually. On the other hand, the conventional treatment with antibiotics can hardly bring about better effect. For example, condyloma acuminatum virus can hardly be treated. In addition, the treatment of urogenital tract infection with Chinese lotion also has disadvantages, for main examples, unremarkable effect, inconvenient use, and contamination of clothing. Hence, a medicament for effectively treating urogenital tract infection is in need all the time.

[0003] In the research of "bio-waves" theory, the present inventor has set up a bacterial wave growth model. Through researching, it is known that this wave is of its intrinsic regulation mechanism: some chemical substances are able to participate the regulation in the bio-wave process, so as to transform an abnormal periodic slow wave into a normal physiological chaotic quick wave, and this kind of substances are known as promoting wave factors. Through separating, purifying and identifying, it is determined that one of the factors is N-acetyl-D-glucosamine, the promoting wave function of which is shown in regulating the coupling oscillation of cellular membrane protein and sugar coating. Many biochemical and physiological process of human body need the participation of the promoting wave factors, and it would lead to an abnormal state, if this kind of promoting wave factors is lacked in the living body.

[0004] N-acetyl-D-glucosamine is a chemical reagent. From the 1990's, it is continually used to treat diseases such as pericementitis (WO9102530A1), intestinal inflammation (WO9953929A1), cornea disease (JP10287570A2), hypertrophy of the prostate (US05116615), organic pathologic changes of lower digestive tract mucous membrane (WO93/14765), etc., as tissue growth regulation agent (WO/8702244), and in cosmetology (JP59013708A2), shampoo preparation (JP2011505A2), etc., but is has not been used in the manufacture of a medicament for treating urogenital tract infection.

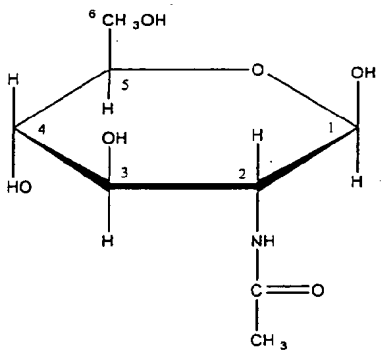
Contents of the invention

[0005] The present invention surprisingly discovers that N-acetyl-D-glucosamine can be used to effective treat urogenital tract infection. This discovery is surprising because the heal of urogenital tract infection needs to control microorganism infection, to treat topical exudation, to eliminate tissue inflammatory edema and pains, to promote tissue repair, and so on, and a doctor usually provides a combination of several medicaments, while N-acetyl-D-glucosamine could be used as the only active ingredient in a medicament for healing urogenital tract infection.

[0006] Based on the above discovery, the present application relates to the use of N-acetyl-D-glucosamine and pharmaceutical acceptable salt thereof in the manufacture of a medicament for treating urogenital tract infection.

[0007] On the other hand, the present invention relates to a method for treating urogenital tract infection, comprising administrating to a patient in need of this treatment an effective amount of N-acetyl-D-glucosamine or a pharmaceutical acceptable salt thereof.

[0008] N-acetyl-D-glucosamine is a compound of the following formula.



[0009] N-acetyl-D-glucosamine is commercially available from market or prepared according to a known method. For instance, WO97/31121 discloses a method for preparing N-acetyl-D-glucosamine from chitin by enzyme method. JP63273493 has discloses a method comprising partially hydrolyzing chitin to obtain N-acetyl-chitose, and then treating it with an enzyme to obtain N-acetyl-D-glucosamine.

[0010] The pharmaceutical acceptable salts of N-acetyl-D-glucosamine that can be mentioned are the salts formed with pharmaceutical acceptable acids, for instance, the salts formed with inorganic acids, such as hydrochloride, hydrobromide, borate, phosphate, sulfate, hydrosulfate and hydrophosphate, and the salts formed with organic acids, such as citrate, benzoate, ascorbate, methyl sulfate, naphthalene-2-sulfonate, picrate, fumarate, maleate, malonate, oxalate, succinate, acetate, tartrate, mesylate, tosylate, isethionate, α-ketoglutarate, α-glyceryl phosphate and glucose-1-phosphate.

[0011] The compound of the formula (I) or its pharmaceutically acceptable salt is used as main active component in combination with several pharmaceutically acceptable excipients and/or carriers to prepare a topical formulation form such as aqua, emulsion, cream, lotion, ointment, suppository, etc. for treatment of urogenital tract infection. The amount of the active component is 0.1 to 10%, preferably 0.2 to 6% relative to the whole formulation. The daily dose of said medicament is 10 to 10000 mg, preferably 50 to 5000 mg, more preferably 100 to 2000 mg of N-acetyl-D-glucosamine per person.

[0012] The composition of the present invention in form of topical formulation, such as solution, emulsion, suspension, viscoloid, cream, ointment, etc. for topically daubing or washing, can be prepared by mixing the active component with one or more pharmaceutically acceptable carriers and additives, such as water, polyethylene glycol, glycerin, Vaseline, xanthan gum, alcohols, etc. as dissolving agent, lubricant, binder, preservative, stabilizer, and in combination with an ecological regulator such as lactic acid according to general techniques as well known by the person skilled in the art. In addition, a propellant can be added to said formulation to prepare an aerosol for topically spraying. For example, an aerosol has a formulation comprising 1 % N-acetyl-D-glucosamine, 3% lactic acid, and 0.3% sodium benzoate.

[0013] Unrestricted to any theory, the inventor deems the effect of the compound of formula (I) of the present invention for treatment of urogenital tract infection is achieved by adjusting the redistribution of body cells. "Cell redistribution" means the continue position alternation of body tissue cells or microorganism cells and the rhythmic alternation of coagulation-dissolution state of biological macromolecules in cells. N-acetyl-D-glucosamine brings about a special function by regulating cell redistribution in different levels. The alternation of macroscopic cell position represents the feature of the cell growth in wave manner. N-acetyl-D-glucosamine regulates the growth of body cells and microorganism cells in normal wave manner, so that microorganisms cannot be topically transplanted. As for microecological function, the normal bacteria growth is supported, and the supplement of ecological bacteria is not employed, so that the disadvantage of adaptability of the supplementary bacteria is avoided. In terms of promoting repair of skin and mucous membrane tissues, the product of the present invention exhibits unique effects for controlling inflammation, damage, infection, and exudation. Thus, the product of the present invention can be widely used for controlling conditions and for essential treatment.

[0014] The following experimental examples are used to illustrate the promoting wave function, low toxicity, activity for suppressing microorganism transplantation, and clinical effect for treatment of urogenital tract infection.

I. Promoting wave test of the compound of formula (I)

1. Experimental materials and method:

1.1 Samples: pure compound of formula (I).

1.2 Experimental materials:

Strain: *Proteus Mirabilis* and *lactobacillus.*

[0015] Culture medium: modified LB culture medium (the components of said medium are: 1% trytones, 0.5% yeast extract, 1% sodium chloride, 0.1% glucose, 0.002% TTC, and pH = 7.2 to 7.4).

1.3 Experimental method:

[0016] The *Proteus Mirabilis* were inoculated at the center of LB plate, incubating at 37°Cfor 9 hours, then there were concentric rings emerged, which were extended outward continually with an interval of 3 hours, and this was taken as a control; adding the compound of formula (I) with final concentration of 0.5% onto the LB plate, the *Proteus Mirabilis* were inoculated by the same method, cultured at 37°C, and the result showed that not only the concentric rings formed with an interval of 3 hours were emerged, comparing with the control, it can be seen that there were also many fine waves on each ring emeraged.

[0017] The liquid culture results showed that the compound of formula (I) could promote the growth of *lactobacillus.*

2. Experimental results and evaluation:

[0018] The experiment adopts a bio-wave model which is used to research the promoting wave function of the compound of formula (I). It can be seen from the result that the compound of formula (I) was not only able to cause bacterial cell to reveal a normal bio-wave characteristic, but also cause the wave reveal finer wave mode, and these indicated that the compound of formula (I) have promoting function to bio-waves, and the promoting wave function is able to participate the repair and redistribution of skin cells.

II. Toxicological test of the compound of formula (I), including:

1. Acute toxicity test: including tests of oral administration, intravenous injection administration, and maximum limit amount for administration;

2. Ames test;

3. Micronucleus test of mouse bone marrow cell;

4. Abnormality test of mouse sperm;

5. Aberration test of mouse testis chromosome;

6. Chronic lethal test;

7. Subchronic toxicity (feed for 90 days) test;

8. Traditional deformity-inducing test.

[0019] The results from these tests showed that in the acute toxicity test of the compound of formula (I), the dosage more that 2 g/kg was taken, which was 300 times than the injection dosage for human being, but the acute toxicosis reaction had not appeared yet; in the long-period toxicity test, the maximum dosage had reached up to 1 g/kg, and after the treatment and observation for four weeks, there was no intoxication reaction yet; and in the reproduction test, the mouse was feed from routine dosage of 7 mg/kg for 3 generations, it had been proved that the compound of formula (I) had no influence on the pregnancy, birth, nurse and the growth of baby mouse, so that the compound of formula (I) is a substance without toxicity.

III. Tests of effect for suppressing bacterial transplantation

1. Test of effect for suppressing *bacillus pyocyaneus* transplantation on skin

2. Test of suppressing bacteria

[0020] The results of these two tests indicated that the compound of formula (I) essentially exhibited no bactericidal or bacteriostasis effect, but it suppressed the transplantation and growth of *bacillus pyocyaneus* so as to achieve the object of anti-infection.

IV. Clinic tests

[0021] 1. 170 patients suffering various venereal diseases were picked out, including 50 patients suffering gonorrhea, 50 patients suffering syphilis, 20 patients suffering *condyloma acuminatum* virus infection, 40 patients suffering *trichomonas vaginalis* infection, and 10 patients suffering *candida albicans*. 2% N-acetyl-D-glucosamine aerosol was topically sprayed to infected areas, and the effects of the compound of formula (I) for treatment of urogenital tract infections were determined by smearing and microscopic examination, and by isolation and culture. The results showed that the effective rate of N-acetyl-D-glucosamine for treatment of various urogenital tract infections is 79% as depicted in the following table.

Observation of therapeutical effect of N-acetyl-D-glucosamine for treatment of urogenital tract infections			
Infection pathogen	Case number	Effective rate (%)	Ineffective rate (%)
Gonorrhea	50	90	10
Syphilis	50	60	40
condyloma acuminatum virus infection	20	80	20
trichomonas vaginalis infection	40	75	25
candida albicans	10	90	10

Industrial applicability

[0022] The present invention pioneers a novel medial use of N-acetyl-D-glucosamine, extends the application range of N-acetyl-D-glucosamine, and increases the use value of N-acetyl-D-glucosamine. The external formulations in various forms prepared with N-acetyl-D-glucosamine as active component are used as medicament for prevention and treatment of urogenital tract infections, and exhibit advantages of easy preparation and no toxic and side effect. Since it is a colorless, insipid and nonirritant substance, and has a novel action route, its use exhibits unique therapeutical effect and avoids disadvantages of other products.

Claims

1. A use of N-acetyl-D-glucosamine and pharmaceutical acceptable salts thereof in the manufacture of a medicament for treatment of urogenital tract infection.

2. The use according to claim 1, wherein said medicament is a formulation in the form for topical administration.

3. The use according to claim 2, wherein said medicament is a formulation in a form selected from a group consisting of lotion, aqua, emulsion, cream, ointment, and suppository.

4. The use according to any one of claims 1 to 3, wherein the daily dose of said medicament is 100 to 2000 mg of N-acetyl-D-glucosamine.

5. The use according to any one of claims 1 to 3, wherein the concentration of N-acetyl-D-glucosamine in said medicament is 0.1 to 10% by weight.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN03/00664

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K31/7008,A61P13/02, 15/00, 31/00, A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K31/7008,A61P13/02, 15/00, 31/00, A61K9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CNPAT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT,WPI,EPODOC,PAJ:acetyl ,glucosamine ,urogenital track,venereal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO02067948A1(UNIV MILITARY MEDICAL NO 3 PLA) see whole document 06-09-2002	1-5
A	WO9953929A1(GLUCOGENICS PHARM INC) see whole document ,28-10-1999	1
A	WO9314765A1 (UNIV BRITISH COLUMBIA)see whole document 05-08-1990	1
A	US05116615A (IMMUNOLYTICS INC) see whole document 26-05-1992	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19.SEP.2003(19-09-2003)	18 DEC 2003 (18.12.03)
Name and mailing address of the ISA/CN 6 Xitucheng Rd., Jimen Bridge, Haidian District, 100088 Beijing, China Facsimile No. 86-10-62019451	Authorized officer Wang Jingjing Telephone No. 86-010-62093910

Form PCT/ISA /210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT
Information on patent family members

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PCT/CN03/00664

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